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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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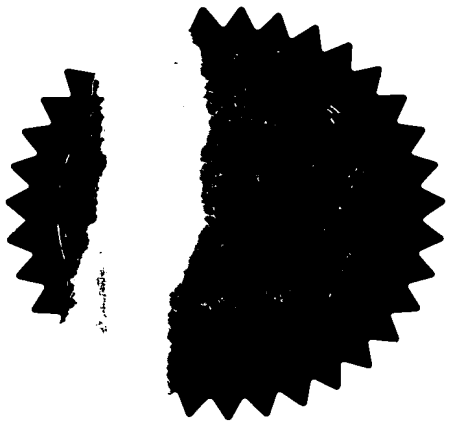

Signed R. Mahoney

Dated 27 June 2003

Patents Form 1/77

ents Act 1977
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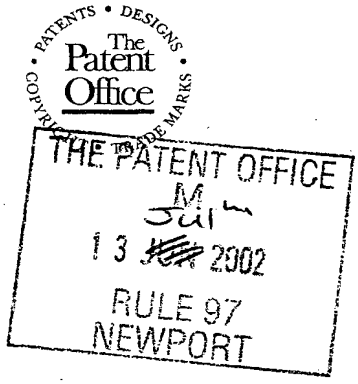


1/77

16JUL02 E735940-1 D00318
P01/7700 0.00-0216311.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

KJL/CT/P5039

2. Patent application number
(The Patent Office will fill in this part)

13 JUL 2002 0216311.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Great Lakes (UK) Limited
Halebank
Widnes
Cheshire
WA8 8NS
United Kingdom

07865181001
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

An improved process for the production of substituted thioxanthones

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ROYSTONS,

Tower Building,
Water Street,
Liverpool. L3 1BA
Merseyside.

Patents ADP number *(if you know it)*

1438001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6 ✓
Claim(s)	-
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature ROYSTONS Royston Date 12/07/02

12. Name and daytime telephone number of person to contact in the United Kingdom

K.J. Lees - 0151-236 3147/1417

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

Title: An improved process for the production of substituted thioxanthones.

DESCRIPTION

The present invention relates to an improved process for the production of substituted thioxanthones.

Various routes for the synthesis of substituted thioxanthones have been described. See, for example, J. Chem. Soc. 1910 (97), 1297, Davis and Smiles; J. Chem. Soc. 1911 (99), 1355, Marsden and Smiles; J. Indian Chem. Soc. 1929 (6), 273, Sen and Sen-Gupta and WO97/49664, Anderson et al. Lambson Fine Chemicals Ltd.

Whilst conventional synthetic routes to substituted thioxanthones are adequate, they do have a number of drawbacks. The routes can result in low yields of the desired product and/or mixtures of isomers and by-products that may be difficult to separate or purify. Thioxanthones with side chains containing a chemically reactive group are conventionally made by further synthetic steps from the thioxanthone molecule and can involve two, three or four stages, resulting in the production of such molecules being a time consuming and inefficient process with low overall yields.

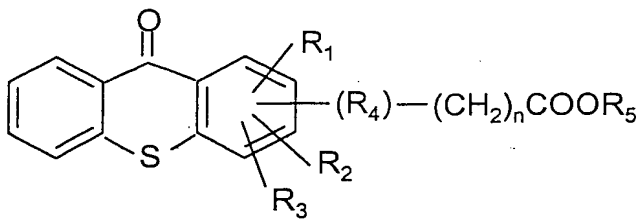
An example of a conventional synthetic route to 2-carboxymethoxythioxanthone involves three stages. Firstly, phenol is reacted with dithiobisbenzoic acid to produce 2-hydroxythioxanthone in a

60% yield. Secondly, the 2-hydroxythioxanthone is reacted with ethyl bromoacetate to produce the ethyl ester of 2-carboxymethoxythioxanthone in 75% yield. Thirdly, the ester is hydrolysed by acidification to produce the desired product in 90% yield. These three stages form an inefficient and time-consuming process to provide a product that is a dark colour, contains impurities and by-products and is produced with only an overall yield of 40% from the starting material.

Substituted thioxanthones with side chains containing reactive groups are important intermediates in the pharmaceutical and photochemical industries. Therefore, an improved process for producing these intermediates in higher yields, with fewer steps and with less impurities would be desirable.

It is object of the present invention to provide an improved process for the production of thioxanthone derivatives containing side chains with chemically reactive side groups that aims to overcome, or at least alleviate, the above-mentioned drawbacks.

Accordingly, the present invention provides a process for the production of thioxanthone derivatives of the general formula (I) given below:



(I)

where:

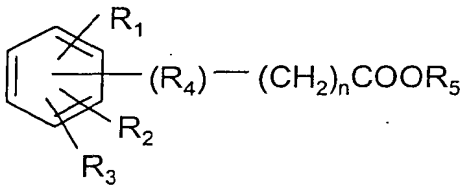
R_1, R_2 and R_3 is hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, halogen, hydroxy or C_1-C_2 dialkylamino; R_1, R_2 and R_3 being the same or different;

R4 is oxygen, sulphur or absent;

n is 0 to 10; and

R_5 is hydrogen, C_1-C_{10} alkyl or aryl;

the one-step process comprising reacting a compound of given general formula (II) below with mercaptobenzoic acid or dithiobisbenzoic acid in the presence of sulphuric acid:



(II)

Preferably, the compound of formula (II) is phenoxyacetic acid, where R_1, R_2, R_3 and R_5 are each hydrogen, R_4 is oxygen and n = 1, thereby producing 2-carboxymethoxythioxanthone.

Preferably, the sulphuric acid is used in amounts of 1 part to about 20 parts by weight of acid to 1 part by weight of dithiobisbenzoic or mercaptobenzoic acid. The concentration of the acid is preferably greater than or equal to 90%.

The molar ratios of dithiobisbenzoic acid or mercaptobenzoic acid to a compound of formula (II) may vary between about 1:1 to 1:5.

Preferably, the reactants are stirred for a sufficient time to complete the reaction. The reaction temperature during the addition of the reactants is preferably in the range 0°C to 30°C but may be increased during the reaction from about 30°C to about 90°C. The reaction time is preferably 0.5 to 6 hours.

The product is preferably isolated from the reaction mixture by quenching with excess water and filtering the solid product. Preferably, water is added to dilute the acid strength to about 20 to 50%. The filtered product may be washed with water. The product may be further purified, if required, by means of crystallisation or slurry in an appropriate solvent.

The resultant thioxanthone compound is substantially free of impurities and may be provided in yields of up to 80%. Additionally, a single isomer is obtained.

The present invention will now be further illustrated by means of the following Examples in which Example 1 describes the synthesis of 2-carboxymethoxythioxanthone from dithiobisbenzoic acid according to the method of the present invention and Example 2 describes the synthesis of 2-carboxymethoxythioxanthone from mercaptobenzoic acid according to the method of the present invention.

Example 1.

The preparation of 2-carboxymethoxythioxanthone from dithiobisbenzoic acid.

Concentrated sulphuric acid (500g) and dithiobisbenzoic acid (30.6g) were charged to a reactor and phenoxyacetic acid (60.8g) was added over 1 hour keeping the temperature at 0-25°C. After stirring for 1 hour, water (470mls) was added. The solid product was filtered and washed with water (2x50mls). The solid was then stirred in 50% aqueous acetone (200mls) and heated to reflux for 0.5 hours. After cooling to ambient temperature the solid was filtered, washed with water and dried. 2-Carboxymethoxythioxanthone (43.4g) was obtained in 76% yield. This was a dull yellow solid, melting point 207 - 212°C. Assay by HPLC >97%. A single isomer was obtained.

Example 2.

The preparation of 2-carboxymethoxythioxanthone from mercaptobenzoic acid.

Concentrated sulphuric acid (250g) and mercaptobenzoic acid (15.4g) were charged to a reactor and phenoxyacetic acid (25.8g) was added over 1 hour keeping the temperature at 5-25°C. The temperature was raised to 50-60°C for 1 hour then water (270mls) was added. The solid product was filtered and washed with water (2x50mls). The solid was stirred in 120mls 50% aqueous acetone and brought to reflux for 0.5 hours. After

cooling to 15°C, the solid was filtered, washed with water and dried. 2-Carboxymethoxythioxanthone (13.5g) was obtained in 47% yield. This was pale yellow solid, melting point 210-215°C. Again, a single isomer of the product was produced.

The present invention enables a substituted thioxanthone compound to be provided that is substantially free of impurities and can be isolated in yields of up to, and possibly in excess of, 80% and as a single isomer.

This invention displays a yield from a single stage process that greatly exceeds that from alternative multi-stage conventional synthetic routes and provides material which is essentially free of impurities. The thioxanthone compounds so produced are useful as reactive intermediates in the pharmaceutical and photochemical industries.